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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,017	02/04/2002	Michael T. Migawa	IBIS-0401	4111

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 12/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	10/067,017	MIGAWA ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 29 November 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ they raise the issue of new matter (see Note below);
   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____.
3. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *2-41 and 44*.

   Claim(s) objected to: _____.

   Claim(s) rejected: *42 and 43*.

   Claim(s) withdrawn from consideration: _____.
8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.
9. ☒ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). 4.
10. ☐ Other: _____

Thomas C. McKenzie, Ph.D.
Primary Examiner
Art Unit: 1624

Continuation of 3. Applicant's reply has overcome the following rejection(s): Applicants' deletion of "heteroalkyl" etc overcomes the indefiniteness rejection to claims 2-34 and 37-44 made in point #2 of the final rejection..

Continuation of 5. does NOT place the application in condition for allowance because: Claims 42 and 43 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating bacterial infections, does not reasonably provide enablement for "administering" the composition generally. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546. To whom is the composition to be given? Is everyone, well or sick to be given the composition?

a) Determining if any particular claimed compound would treat every human disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with every different human disease, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a huge degree of experimentation. b) There is no direction concerning treating any diseases found in the specification. Applicants describe formulations in the passage spanning line 4, page 15 to line 2, line 30. There are no working examples of any formulation anywhere in this lengthy passage. Applicants do not teach the doses required to practice their invention anywhere in the specification. Since no compound has ever been used to treat every human disease, how is the skilled physician to know what dose to use for each of these different diseases? There is are in vitro assays drawn to 8 bacteria and 1 fungus species described in the passage spanning line 15, page 61 to the end of page 71. None of the tables of data are labeled with the microorganism used, so how is the physician to know which compound to use with which bacteria? A Table 3 is mentioned but is missing from the specification. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts is that no compound has ever been found that will "give a desired result" with every known disease.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the thousands of compounds of claim 1 as well as the uncounted number of diseases embraced by the claim. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Applicants argue that determining to whom the "pharmaceutical composition" is to be administered, "in a pharmaceutically acceptable manner" is not a claim limitation. Applicants then argue that little skill is required in physically administering the shots or pills containing Applicants' compounds. This is not persuasive because inherent in the words "pharmaceutically" and pharmaceutical" is the intent to treat a disease. Broadly interpreted the present claim reads on treating all diseases and reads on administering to subjects who are well. It reads on administering this to people infected with bacteria as well as every other human disease. The MPEP in §2111 requires the Examiner to give the claim the, "broadest reasonable interpretation". The how to make rejection hinges on the clinical efficacy of Applicants' compositions for treating disease not on the ease or difficulty of the actual administration. The claim as broadly interpreted is simply not operable and the claimed treatment process will not work in the vast majority of people to whom the claim covers.

DETAILED ACTION

1. This action is in response to amendments filed on 11/29/04. Applicant has indicated that claims 2-36 and 44 have been amended. Claims 2-34 and 37-44 were previously rejected. Claims 2-41 and 44 were designated as containing allowable subject matter. There are forty-three claims pending and forty-three under consideration. Claims 2-37 and 44 are compound claims. Claim 38 is a composition claim. Claims 42 and 43 are method of using claims. Claims 39-41 are method of making claims. This is the fourth action on the merits. The application concerns some antibiotic cytosine nucleoside analogue compounds, compositions, and uses thereof. Although claims 4-6, 8-10, 12-14, 16-18, 20-22, 24-26, 28-30, and 32-34 are indicated as amended, the Examiner can see no changes.

Response to Amendments

2. Applicants' deletion of "heteroalkyl" etc overcomes the indefiniteness rejection to claims 2-34 and 37-44 made in point #2 of the final rejection.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42 and 43 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating bacterial infections, does not

reasonably provide enablement for "administering" the composition generally. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. To whom is the composition to be given? Is everyone, well or sick to be given the composition?

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formulations in the passage spanning line 4, page 15 to line 2, line 30. There are no working examples of any formulation anywhere in this lengthy passage. Applicants do not teach the doses required to practice their invention anywhere in the specification. Since no compound has ever been used to treat every human disease, how is the skilled physician to know what dose to use for each of these different diseases? There is are *in vitro* assays drawn to 8 bacteria and 1 fungus species described in the passage spanning line 15, page 61 to the end of page 71. None of the tables of data are labeled with the microorganism used, so how is the physician to know which compound to use with which bacteria? A Table 3 is mentioned but is missing from the specification. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts is that no compound has ever been found that will "give a desired result" with every known disease.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h)

The scope of the claims involves all of the thousands of compounds of claim 1 as well as the uncounted number of diseases embraced by the claim. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

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Allowable Subject Matter

4. Claims 2-41 and 44 are allowed.